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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,183	GYURIS ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2004 and 09 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-33,54-88 and 93-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-33,54-88 and 93-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/06/2004 has been entered.

Claims 28, 54, 55, 80, and 87 are amended. Claims 28-33, 54-88, and 93-104 are pending. Claims 28-33, 54-88, and 93-104 are examined on merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

This Office action contains new grounds of rejection.

Claim Rejections - 35 USC § 112, Withdrawn

The rejection of the claims under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is **withdrawn** in view of scope of enablement rejection below.

Claim Rejections - 35 USC § 102, Maintained

Claims 28, 54-56, 58-62, 64-77, and 93-104 remain rejected, and claims 29, 32, 80-83, and 85-88 are newly under 35 U.S.C. 102(b) as being anticipated by WO 95/30759 of record (Publication date Nov. 6) as evidenced by Fixe et al., of record

(1998, Cytokine vol. 10, pages 32-7, note IDS filed on 4/30/03) and Castells (1994, Allerg Immunol, vol. 26, pages 127-31, abstract only).

Fixe et al., of record and Castells are used to explain the functional details of the inserted heterologous peptide of the 95/30759. Castells is added in this Office action to explain further about the nature of MIRR in claim 62 since the art i.e. WO 95/30759 and the instant application use different terminology to mean a single entity.

Claims 28, 29, 32, 54-56, 58-62, 64-83, and 93-104 are interpreted as drawn to a nucleic acid encoding a chimeric polypeptide comprising a serum albumin (SA) with a biologically active heterologous peptide inserted anywhere into said SA (independent claim 28), inserted in the middle of SA (independent claims 54, and 55), at least two biologically active heterologous peptides inserted anywhere into said serum albumin (independent claim 80), wherein the chimeric polypeptide exhibits increased biological activity relative to the heterologous peptide sequence itself, and interacts with a living organism to induce a change in a biological function of the organism or any part of the organism (all claims), wherein the nucleic acid is a delivery vector (claim 29), wherein the delivery vector is inside a cell (claim 32), wherein the heterologous peptide is a fragment of an angiogenesis-inhibiting protein (claims 56), wherein the peptide binds to a cell surface receptor protein (claim 58), wherein the receptor protein is a G-protein coupled receptor (claim 59), a tyrosine kinase receptor (60), a cytokine receptor (claim 61), a MIRR receptor (claim 62), wherein the chimeric polypeptide binds to an extracellular receptor (claim 64), is an agonist (claim 65), or antagonist (claim 66), induces apoptosis (claim 67), modulates cell proliferation or differentiation (claims 68,

and 69), wherein the size of the heterologous peptide inserted could be anywhere from 4 to 400 amino acids (claims 70-73, 93-104), wherein the tertiary structure of the chimeric polypeptide is similar to a native SA (claim 74), wherein the inserted peptide sequence replaces a portion of the native SA (claims 75), or replaces a portion of a cysteine loop (claim 87), wherein the inserted sequences and replaced portion of native SA sequence are unequal length (claim 76), wherein the chimeric polypeptide of the base claims 28, 54, or 55 is at least 10-1,000 times more active than the biologically active peptide sequence before the insertion into SA (claims 77-79), wherein at least two biologically active peptide sequences specified in claim 80 are identical (claim 81), wherein at least two biologically active peptide sequences comprise distinct sequences of a protein (claim 82), comprises sequences from at least two different proteins (claim 83), wherein the heterologous peptide sequence is inserted in a cysteine loop (claim 85), or into the specifically recited cysteine loops (claims 86, and 88).

In the response filed on 02/06/2004, beginning bottom of page 12 to page15, applicant argues that the cited references fail to teach all limitations of claimed invention, and also fail to anticipate the claimed invention inherently.

Since the instant application does not disclose any new "biologically active peptide" being inserted in SA, nor discloses any new SA, and applicant's argument is mostly about the '759 publication not teaching the limitation "increased biological activity" of the peptide in SA as compared to the peptide before the insertion into SA, the main focus of the 102 (b) analysis is to determine whether the '759 publication teaches "increased biological activity" of the chimeric SA.

Applicant at the paragraph bridging pages 12 to 13, states that the claimed invention is directed to a chimeric SA polypeptide that "exhibits increased biological activity relative to the heterologous peptide sequence itself (emphasis added)". From page 13 to second paragraph of page 15, applicant argues that the '759 publication is completely silent about the chimeric proteins actually having any biological activity of the inserted peptide, much less about chimeric proteins actually having increased biological activity relative to the inserted peptide, but merely hopes that a chimeric polypeptide might possess at most, enhanced stability, which the '759 publication never shows. Furthermore, even if the publication teaches enhanced stability, enhanced stability is still different from increased biological activity.

However, the arguments appear to be contrditory to applicant's earlier statement about applicant's claimed invention disclosed in this application "**The Office Action seem to have misinterpreted the claimed invention which is partly directed to the discovery that serum albumin serve as a 'protein carrier' to a heterologous polypeptide inserted herein, and confers the inserted heterologous polypeptide an increased lifetime (half-life), and thus increased observed biological activity relative to the uninserted heterologous polypeptide (for example, see paragraph bridging at page 5 and 6).**" Note 2nd paragraph of page 14 of the amendment filed on 07-05-2002. Thus, the prosecution history shows that applicant has argued that the full scope of the claimed invention encompasses "**increased lifetime (half-life), and thus increased observed biological activity relative to the uninserted heterologous polypeptide**". Applicant in the response filed on 02/06/2004 appears to argue

inconsistent interpretations of the scope and contents of the claims as compared to the earlier statement about the nature of the claimed invention.

Applicant also argues at page 13 "Contrary to assertions in the Office Action, the claimed invention is not limited to those of polypeptide exhibiting a 1000-fold increase in biological activity but more generally to those exhibiting increased biological activity when compared to the heterologous peptide before inserting said peptide into SA." This argument appears to be in response to the Office action mailed on 11/04/2003 at bottom of page 3, which stated:

> Applicant argues that EC binding peptides inserted in SA exhibits 1000-fold more activity and the art does not show this dramatic increase as shown at page 44 of the specification. However, these arguments are not persuasive because the claims are not limited to the specific structure.

As shown above, the Office did not assert that the claimed invention is limited to chimeric SA exhibiting a 1000-fold increase in biological activity, but the statement above means that applicant's previous argument with the EC binding peptide inserted in SA is not commensurate in scope of the claims because the full scope is not limited to the specific structure that applicant is now arguing with.

Applicant at page 13, 1st paragraph argues that the instant specification at page 44 (the Office assumes applicant meant page 41, instead of page 44 since page 44 of the specificaion has claims 9-19), 2nd paragraph teaches one example, a synthetic EC binding peptide inserted into mouse serum albumin has 1000-fold higher biological activity than the synthetic binding peptide alone. This argument is not persuasive because the argument is not commensurate in scope of the claims. Further, the RGD sequence used as the control in the assay at page 41 is a cyclied RGD peptide (note 2nd paragrph under the heading "BCE Proliferation Assays"), whereas the RGD

sequence inserted in MSA is a linear peptide. This conclusion is made because the specificaiton does not teach how to insert a cyclic RGD sequence directly into a SA. The instant application at pages 13 and 14 discloses that making the claimed chimeric polypeptide could be complished using the art-known recombinant DNA technology. Thus, comparison of a cyclic RGD vs. a linear RGD in SA do not seem to fit the description of the limitation "a serum albumin (SA) having **a biologically acitve heterologus peptide seqeunce** inserted therein, wherein the chimeric polypeptide exhibits increased biological activity relative to **said peptide sequence** itself", because the claims 28, 54, and 55 compare a linear peptide to said linear peptide inserted in SA. Note the first mentioned heterologus peptide and the second mentioned heterologus peptide in claims 28, 54, and 55 should be same. However, the 1000-fold inreased activity in the in vitro binding assay is comparing a cyclic peptide with a linear peptide in SA. Therefore, the argument with the RGD sequence is considered with arguing a limitation not present in the claims.

Applicant at page 14 argues that the '759 publication describes a hypothetical chimeric SA containing a clevage site for the factor Xa protease at amino acid 58. No data or evidence is provided in this hypothetical example or anywhere else in the '759 reference that any insertions in albumin result in chimeric proteins that retain any of the biological activity of the inserted peptide, much less having increased biological activity. Accordingly, the '759 publication teaches no working examples of chimeric SA proteins having any of the biological activity of the inserted peptides. The '759 publication merely presents, at most, an exercise in standard cloning techniques. Because the '759

publication does not teach chimeric SA proteins having an increased biological activity relative to the inserted peptide, and reference to Zetter or Fixe does not correct this defect, the cited references fail to teach every limitation of the claimed invention, and therefore they do anticipate the claimed invention. Applicant at page 15 cites MPEP 2112 and Ex Parte Levy for inherency analysis. Applicant argues that enhanced half-life is not same as increased biological activity, the '759 publication at best enables a skilled artisan to make and use a chimera of increased half-life, but does not teach or suggest that an inserted heterologous polypeptide may exhibit an unexpectedly increased biological activity: neither Zetter nor Fixe correct this defect. These arguments have been fully considered but found unpersuasive for the following reasons.

The specification as originally filed does not disclose that "increased half-life in serum" is not same as "increased biological activity". In other words, the instant application as originally filed does not disclose that enhanced stability and increased biological activity are different as applicant now argues. In fact, the specification as originally filed at 2nd line of the abstract discloses the invention is a nucleic acid encoding "The chimeric polypeptides may exhibit therapeutic activity related to the heterologous peptide sequences coupled with the improved serum half-lives derived from the serum albumin protein fragments." The abstract of the instant application clearly dislcoses that the nature of the claimed invention has to do with the improved **serum half-lives** of a therapeutic peptide when inserted in a SA. Thus, the broadest reasonable interpretation of the claimed invention as a whole encompasses improved stability by inserting a heterologous peptide into a carrier protein SA.

Since applicant duriing the prosecution history has argued inconsistent interpretations of the scope and contents of the claims, and the specification as originally filed does not define that increased stability is NOT increased biological activity as applicant now argues, the Office is forced to turn to the art for guidence to determine meaning of "incrased biological activity" understood in the current state of art.

US 6,288,234 B1 (Sept. 11, 2001) at column 21, lines 8-16 discloses:

> The phrase "increased biological or therapeutic effect" includes, for example: increased affinity, increased selectivity for target, increased specificity for target, increased potency, increased efficacy, decreased toxicity, improved duration of activity or action, decreased side effects, increased therapeutic index, improved bioavailibity, improved pharmacokinetics, improved activity spectrum, and the like.

US 6,288,234, published around the time the instatn application was filed suggests that "improved bio availability", and/or "improved duration of activity or action" due to increased in vivo half-life is "increased biological activity": this disclosure is same as applicant's earlier statement that "the claimed invention which is partly directed to the discovery that serum albumin serve as a 'protein carrier' to a heterologous polypeptide inserted herein, and confers the inserted heterologous polypeptide an increased lifetime (half-life), and thus increased observed biological activity relative to the uninserted heterologous polypeptide". Note 2nd paragraph of page 14 of the amendment filed on 07-05-2002. Thus, based on meaning of "increased biological activity" as understood in the art, the broadest reasonable interpretation of the claimed invention as a whole in light of the disclosure in the specification, the interpretation of the claimed invention in light of the prosecution history, it is thus concluded that the '759 publication which discloses at page 6 "promoting the bioavailability and in vivo stability" of a

therapeutically useful peptide by inserting the therapeutically useful peptide into a carrier protein SA, is an art that anticipates instant claims 28, 29, 32, 54-56, 58-62, 64-83, and 93-104. It is noted that neither the instant specification nor the prior art i.e. WO 95/30759 has any working example of in vivo increased biological activity.

WO 95/30759 teaches a nucleic acid (see Fig. 3, 5, 6, pages 26-30, for example), and delivery vector (see claim 26) encoding a chimeric polypeptide comprising serum albumin with a useful heterologous peptide inserted preferably in "exposed regions" of serum albumin with the various construction methods described in the instant claims 28, 54, 5574, 75, and 76 (note Fig. 2, page 5-10 of the '759 patent).

The '759 patent teaches at page 6, lines 3-6 that the size of peptide inserted could range 1-100 residues. This teaching anticipates the limitation of instant claims 70-73, and 93-104.

The '759 patent teaches at page 7 the preferred insertion sites i.e. exposed regions, which emcompasses for example, residues 57-62 of human serum albumin, which overlapps with Cys53-Cys62 for example, specified in the instant claims 85-88.

The '759 patent teaches at pge 8 " the active part of a biologically active peptide can be repeated several times in the chimeria at the same palce and/or in different regions of the albumin. Moreover, it is also possible to insert different parts according to the invention, either from the same peptide or from different peptides"; this anticipates the limitations of instnat claims 80-83.

The '759 patent teaches the useful heterologous peptides could be derived from various therapeutically useful proteins including an angiogenesis-inhibiting proteins (see

"tumoral angiogenesis" at page 4 line 9) or peptide fragments that bind to tyrosine kinase receptor with various in vivo functional properties (see abstract, page 1-5, last three lines of page 7 to line 7 of page 9, Fig. 1-6, pages 26-30, claims 1-14, 18, 25, and 26). WO 95/30759 also teaches the chimeric polypeptide comprising serum albumin increases in vivo stability and has other desirable pharmacological properties (see page 1). WO 95/30759 teaches various therapeutically useful peptides in claims 3 and 4, at pages 3 and 4, thus covers all of the inserted peptides with either function or name in instant claims 56, 58-62, 64-69. For example, M-CSF (a cytokine, see page 3 of WO 95/30759) binds to a cell surface tyrosine kinase receptor, more specifically bind to an extracellular domain M-CSF-R according to Fixe et al., of record. It is well known in the art before the effective filing date of the instant application that M-CSF is a tyrosine kinase receptor, which involves a signaling in vivo with other G-proteins. Note the description of G-coupled receptor at page 32 of the instant specification as compared to page 32, left column, under the heading "*Synthesis and structure of the M-CSF receptor (M-CSF-R)* of Fixe et al., of record. Thus, a biologically active recombinant polypeptide essentially consisting of at least one active portion derived from M-CSF (see line 7 from the bottom of page 3 of the '759 patent) inserted into SA would bind to a tyrosine kinase receptor protein (i.e., M-CSF-R), and to an extracellular domain of M-CSF-R.

"An antibody" at page 3 or "antibodies" in claim 3 of the '759 patent anticipates the limitation "MIRR" in instant claim 63 because MIRR is multi-chain immune recognition receptor according to Castells (1994, Allerg Immunol, vol. 26, pages 127-31).

"Antagonist or agonist peptide" at page 4 WO 95/30759 anticipates instant claims 65 and 66. The various functional characteristic in instant claims 67-69 for example is an inherent property of the various heterologous peptides in claims 3 and 4 of WO 95/30759.

It is the Office's position that the structure of the chimeric SA encoded by the instantly claimed nucleic acid and the structure of the chimeric SA taught by the prior art are same, therefore the recited increased activity in instant claims 77-79 is the inherent property of the chimeric SA of the prior art. See above for what is encompassed by "increased activity" discussed.

The '759 patent discloses that pharmaceutical compositions comprising a heterologous peptide or protein capable of binding to a tyrosine kinase (M-CSF) recetor; this pharmaceutical would inherently bind to a tyrosine receptor in vivo. Further, inherent in pharmaceutical is in vivo use, thus the peptide in the pharmaceutical comprising the chimeric SA must interact with a living organism to induce a change in a biological functions of the organism or any part of the organism: if it does not interact with a living organism to induce a change in a biological functions of the organism or any part of the organism, then it is not a pharmaceutical.

In summray, the '759 patent teaches all the necessary DNA recombinant technology and other steps to make and use the instantly claimed nucleic acid expressing a chimeric SA polypeptide, for example, protein expression in yeast cells containing the vector expressing the chiemric SA. The strucutre claimed in the instant claims and the structure disclosed in the '759 are same, therefore, the chimeric SA

polypeptide of the '759 patent inherently has all the functional properties as recited in the instant claims as discussed above.

The '759 patent teaches at page 6 lines 11-13 that structure of the albumin cannot undergo too much destabilization. This teaching is seen as anticipating the limitation of instant claim 74 because the claimed structure and the structure of the prior art appear to be same i.e. the overall structure of chimeric SA should be similar.

Any rejection set forth in the Office action mailed on 11/04/2003, but not repeated here in this Office action under 102 (b) is withdrawn in view of the new rejection under 35 U.S.C. 103(a) or under 35 U.S.C. 112 below.

Claim Rejections - 35 USC § 103, Withdrawn

On reconsideration, the rejection of claims 29-33 under 35 U.S.C. 103(a) as being unpatentable over WO 95/30759 (Publication date Nov. 6, 1995, IDS AB filed on July 5, 2002, Paper No. 13) as applied to claims 28, 54, and 55 above, and further in view of admission in the specification at pages 16-22 is **withdrawn**.

The rejection of claims 80-84 under 35 U.S.C. 103(a) as being unpatentable over WO 95/30759 (Publication date Nov. 6, 1995, IDS AB filed on July 5, 2002, Paper No. 13) as applied to claims 28, 54, and 54 above, and further in view of Cardarelli et al, J Biol Chem 1992 Nov 15;267(32):23159-64 is **withdrawn** in view of the new rejection below and new rejection of claims 80-83 above under 35 USC § 102 (b) above.

The rejection of claims 85-88 under 35 U.S.C. 103(a) as being unpatentable over WO 95/30759 (AB of IDS, Paper No. 14, publication date: 11/16/1995) as applied to claims 28 above in view of Carter et al (1994, Advances in Protein Chemistry, vol. 45, pages 153-203, IDS AE filed on July 5, 2002, Paper No. 12) is **withdrawn** in view the rejection under 35 USC § 102 (b) above.

Double Patenting, Maintained

Claims 28-33, 54-84, 93-104 remain provisionally rejected and claims 85-88 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-33, and 49-91 of copending Application No. 09/619,285. Claims 28-33, 54-84, 93-104 remain rejected for reason of record, and it is noted that applicant will file a terminal disclaimer.

Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 85-88 are drawn to Cys 360-369 as the insertion sites and claim 28, for example of copending Application No. 09/619,285 also recites Cys 360-369 as the insertion site.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 112

Claims 28-33, 54-88, and 93-104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28, 54, and 55 recite "increased biological activity", but it is not clear what the metes and bounds are. The specification neither defines what is "increased

biological activity" nor teaches how to measure it with a reasonable certainty. Thus, the scope of the claims becomes ambiguous and indefinite based on applicant's conflicting statements in respect to the scope of the claimed invention as defined by the limitation "increased biological activity". Applicant previously argued at 2nd paragraph of page 14 of the amendment filed on 07-05-2002, "The Office Action seem to have misinterpreted the claimed invention which is partly directed to the discovery that serum albumin serve as a 'protein carrier' to a heterologous polypeptide inserted herein, and confers the inserted heterologous polypeptide an increased lifetime (half-life), and thus increased observed biological activity relative to the uninserted heterologous polypeptide (for example, see paragraph bridging at page 5 and 6)". This statement appears to indicate that "increased biological activity" includes increased in vivo stability. However, applicant now argues that "increased biological activity" and increased in vivo stability are different. Thus, the scope of the claims is ambiguous and indefinite. This rejection affects all dependent claims.

Claim 74 recites "similar" in line 2 but it is not clear what the metes and bounds are for the limitation. The term "similar" appears to be relative, subject to a different interpretation by a different person.

Claim 80 recites "at least one biological active peptide sequence exhibits increased biological activity relative to said one biologically active peptide sequence itself" in lines 3 and 4, but it is not clear what the metes and bounds are. For the purpose of this Office action, the Office will assume the ambiguous and indefinite recitation to mean the chimeric polypeptide encoded by the claimed nucleic acid

exhibits increased biological activity relative the heterologous peptide before the insertion of said peptide into the carrier protein of SA. However, this treatment does not relieve applicant the burden of responding this rejection.

Claim 84 recites the limitation "the myc epitope" and "the RGD peptide" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claims 86, and 88 are rejected because they recite several specific cysteine residues without any reference frame. This is reinstatement of the rejection set forth in Paragraph 11 at pages 4 and 5 of the Office action mailed on 4/2/2002. Applicant argued at page 13 of the amendment filed on 07/05/2002 that the drawing part of the specification illustrates the 3-D space-filling model of human serum albumin; Figures 4A-4I illustrate the position (on the 3-D model) of the claimed cysteine loop regions of mouse serum albumin aground the Cys53-Cys62 loop, with Cys53 and Cys62 marked in bold; the protein sequences of the highly conserved human and mouse serum albumin are well known in the art before the filing of the instant application as evidenced by the GenBank entry shown in Exhibit A; thus, in both human and mouse serum albumins, residues 53, 62, 75, 91, 90, 101, 245, 253, 266, 279, 360, 369, 461, 477, 476, 487, 558, 567 are all known to be cysteins, therefore the instant application unequivocally provides unique identification for amino acid positions recited in the claims. This argument has been fully considered but not persuasive for following reasons.

The scope of the claimed invention is not limited to human or mouse serum albumin but the instant application at page 10, 1st paragraph defines the limitation

serum albumin as "intended to include (but not necessarily to be restricted to) serum albumin proteins of living organisms, preferably mammalian serum albumins, even more preferably known or yet-to-be-discovered polymorphic forms of human serum albumin (HSA), and variants thereof." Claim 86 depends on claim 85, which in turn depends on claim 28, 54, or 55. Serum albumin of claim 28, 54, or 55 is not limited to human or mouse known serum albumin sequence. However, the specification does not reasonably teach which amino acids of a serum albumin sequence is a reference sequence.

Carter and He of record (IDS AE filed on 07/05/2002, 1994, Advanced in Protein Chemistry 45, pages 153-203) at page 160, lines 4-9 teach that there are more than one nomenclatures being used for various serum albumins and the authors of the review article define that the residue designation of serum albumin is normalized to HSA (human serum albumin). Peter, T (1985, Adv Protein Chem. vol. 37, pages 161-245) at Figs. 1 and 2 (page 168-170) teaches that bovine serum albumin is shorter than the human serum albumin by three amino acids, two of the three lie in what is commonly known as cysteine loop 3 (see Fig. 2). Thus, human serum albumin Cys360-Cys369 corresponds to bovine Cys358-Cys367. Therefore, one would have difficulty to determine whether inserting a biologically active peptide into the bovine Cys358-Cys359 would infringe on the instantly claimed invention. Even if the instantly recited cysteine loops refer to a mature human and mouse serum albumin protein sequences, applicant's terminology in the instant specification is not consistent with that of art because Peter, T (cited) above teaches that the mature human serum albumin does not

have cysteine residues at amino acid #266 as indicated in claims 86, and 88 but amino acids #266 is glutamic acid (E). The specification does not disclose that the instant applicant discovered a new human serum albumin with a cysteine residue at #266.

Claims 28-33, 54-88, and 93-104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid encoding the a chimeric SA with exposed regions of a SA as the insertion sites of a heterologous therapeutically useful peptide for making said chimeric SA for increased bioavailability and/or increased stability, does not reasonably provide enablement for the buried regions of a serum albumin, gene therapy construct, or increased biological activity generally (other than increased bioavailability and/or increased stability). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This enablement rejection has several aspects.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

First, this enablement rejection is made because claims 30-33 recite several retrovirus vectors, such as HIV and also recite cells (see claims 30 and 31 for vector, and claim 33 for cells) not commonly used in the art for in vitro protein expression, therefore at least one aspect of the claimed invention as claimed in claims 29-33, 93, 94 for example, are interpreted as drawn to gene therapy.

The instant specification at pages 37-42 is about residues 360-369, especially between residues 364 and 365 is exposed to solvent. The specification does not teach method of gene therapy. The art recognizes that gene therapy is not a trivial matter. The specification does not teach any method of overcoming numerous technical difficulties the art has been facing in the gene therapy art. For example, Friedmann (Scientific American, June 1997, pages 96-101), Verma and Somia (1997, Nature, vol. 389, pages 239-242), and Rubanyi (2001, Molecular Aspects of Medicine 22, pages 113-142) all teach that gene therapy art still faces major hurdle to overcome. Rubanyi at the abstract teaches that the prerequisite of successful gene therapy includes "therapeutically suitable genes with a proven role in pathophysiology of the disease". The instant specification fails at this first prerequisite because the specification does not teach any therapeutically suitable gene with a proven role in pathophysiology of the disease. Verma and Somia teach at page 240, first column that critical limitation of retroviral vectors is their inability to infect non-dividing cells such as muscle cells claimed in instant claim 33. The specification does not teach how to use the retroviral vectors in instant claim 31 for the various cells in claim 33. Friedman summaries the current state of gene therapy as "treating disease by providing needed gene remains a

compelling idea, but clinical and basic researchers still have much to do before gene therapy can live up to its promise" (note the italicized headline at the top of page 96). The instant specification does not teach a single technical problem being solved for the gene therapy art.

Second, the claimed invention is interpreted as drawn to a chimeric polypeptide comprising a chimeric serum albumin with an inserted biologically heterologous peptide buried in said serum albumin. The specification at page 39 discloses that when a heterologous peptide inserted in SA at residues 450-463, the heterologous peptide is buried and therefore inaccessible. The specification does not teach how to use the buried heterologous peptide in a chimeric SA. When the heterologous peptide is buried in serum albumin, it does not appear to exert its biological activity. WO 95/30759 at page 6 teaches that one critical element for chimeric serum albumin is accessibility of the inserted heterologous peptide. Thus, a heterologous peptide inserted by replacing a portion of Cys461-Cys477, for example, inserting said peptide by replacing Cys461 would result in a chimeric SA with the inserted peptide buried in SA, thus inaccessible.

Third, one part of the claimed invention (see for example, claim 58) is interpreted as drawn to nucleic acid comprising chimeric serum albumin inserted with a useful ligand binding peptide to an orphan receptor. Bresnick et al., (2003, Assay Drug Dev Technol. Vol. 1, pages 239-49, abstract only) teach that "orphan receptor" by definition is a receptor without a known ligand. The specification does not teach how to make a biologically heterologous peptide that binds to an orphan receptor. It is noted that law

requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Fourth, this part of enablement rejection is based on the interpretation of the claims 28-33, 54-88, and 93-104 drawn to nucleic acid encoding a chimeric SA with a heterologous peptide, wherein the heterologous peptide in SA has higher biological activity other than increased bioavailability due to increased half-life and/or increased serum half-life in vivo. WO 95/30759 teaches that the main reason, a therapeutically useful heterologous peptide is inserted in SA is that that the resulting chimeric SA has increased in vivo half-life and/or promote bioavailability. See abstract and page 1 WO 95/30759. Likewise, Syed (Blood, 1997, vol. 89, pages 3243-3252) teach insertion of a therapeutically useful peptide in SA results in increased in vivo half-life.

The instant application does not disclose how to make a nucleic acid encoding a chimeric SA, exhibiting increased biological activity more generally when compared to the heterologous peptide before inserting said peptide into SA.

The instant specification at page 41 discloses RGD in SA has higher in vitro binding activity as compared to the cyclied RGD peptide (note 2nd paragrph under the heading "BCE Proliferation Assays). However, comparison of a cyclic RGD vs. a linear RGD in SA do not seem to fit the description of the limitation "a serum albumin (SA) having **a biologically acitve heterologus peptide seqeunce** inserted therein, wherein the chimeric polypeptide exhibits increased biological activity relative to **the heterologous peptide sequence** itself", because the claims 28, 54, and 55 compare a linear peptide to said linear peptide inserted in SA. Note the first mentioned heterologus

peptide and the second mentioned heterologus peptide in claims 28, 54, and 55 should be same. Further, even if the Office accepts this as the inreased activity other than increased in vivo half life, this finding i.e. increased binding of RGD in SA as compared to the cyclic peptide appears to be an exception, not a norm. The specification does not teach whether the increased binding is expected with any binding peptide or this exceptional binding occurred due to the nature of the heterologous peptide and/or the SA being used. In other words, the specification does not teach how to make a nucleic acid encoding a chimeric SA such that more generally increased biological activity of a chimeric SA (other than increased in vivo half-life) would be expected.

Considering the unpredictable state of art, limited guidance, no examples in the specification how to use a chimeric SA with a buried heterologous peptide or how to use gene therapy construct, how to make a construct with more generally increased biological activity of a chimeric SA (other than increased in vivo half-life) that would result in and broad breath of the claims, it is concluded that undue experimentation is required to practice the full scope of the invention.

Claims 28-33, 54-88, and 93-104 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 28-33, 54-88, and 93-104 are interpreted as drawn to genus of nucleic acid molecules encoding chimeric SA polypeptides exhibiting **increased** biological activity.

This reinstatement of written description rejection is made due to the limitation "increased biological activity" of the chimeric SA encoded by the claimed nucleic acid, vector containing said nucleic acid, or produced by cell containing said vector. This restatement of written description rejection is especially made in view of applicant's argument in the response filed on 02/06/04 that increased biological activity is not the same as enhanced stability (note page 13, line 5).

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In this case, the only factor present in the claim is "increased biological activity relative to said peptide sequence itself". There is not even identification of any

particular portion of the structure of either SA or the heterologous polypeptide that must be conserved in order to achieve the recited function. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The art, (note the '759 patent of record, and Syed et al., cited above) teaches that increased in vivo half life is expected when a heterologous peptide is inserted into SA.

It is noted that the specification does not disclose any in vivo increased biological activity of a chimeric SA. The specification at page 41 discloses RGD in SA has higher in vitro binding activity as compared to the cyclied RGD peptide (note 2nd paragrph under the heading "BCE Proliferation Assays). However, comparison of a cyclic RGD vs. a linear RGD in SA do not seem to fit the description of the limitation "a serum albumin (SA) having **a biologically acitve heterologus peptide seqeunce** inserted therein, wherein the chimeric polypeptide exhibits increased biological activity relative to **the heterologous peptide sequence** itself", because the claims 28, 54, and 55 compare a linear peptide to said linear peptide inserted in SA. Note the first mentioned heterologus peptide and the second mentioned heterologus peptide in claims 28, 54, and 55 should be same. Further, even if the Office accepts the data with MSA-the RGD as the inreased activity other than increased in vivo half life, this finding i.e. increased binding of RGD in SA as compared to the cyclic peptide appears to be an exception, not a norm. The specification does not teach whether the increased binding is expected with any binding peptide or this exceptional binding occurred due to the nature of the heterologous peptide or the SA being used. In other words, the specification does not

describe the strucutre of the claimed nucleic acid with more generally increased biological activity other than the MSA-the RGD. The specification does not describe the structure of a nucleic acid molecule encoding a chimeric SA exhibiting increased biological activity when compared to the heterologous peptide before inserting said peptide into SA.

Applicant at pages 18-23 of the response filed on 07/05/2002, especially at page 21 argued that the disclosure in the instant application meets the written requirement because the specification describes increased in vivo half-life. Applicant in the response filed on 02/06/2004 and the response filed on 07/05/2002 contradict each other. Applicant during the prosecution history has argued inconsistent interpretations of the scope and contents about the nature of the claimed invention depending on the rejection at hand. The scope and nature of the claimed invention should be same whether art rejection or written description is at issue.

Applicant at pages 21-22 in the response filed on 07/05/2002 argued that the specification has literal support for all of the heterologous peptides in the claims. However, the written description rejection is NOT about whether the specification as originally filed has literal support for all of those numerous heterologous peptides listed in the claims. Rather, this written description is about whether the specification describes a genus of the claimed structures with the recited function i.e. "increased biological activity" as applicant now argues in traversing the art rejection ("increased biological activity is not the same as enhanced stability", note page 13, line 5 of the response filed on 02/06/04).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of nucleic acid molecules encoding chimeric SA with increased biological activity, given that the specification has at best described the specific MSA with the specific RGD sequence. Therefore, only isolated nucleic acid comprising MSA-the RGD as described at page 42 of the specification, along with the art-taught chimeric SA with increased in vivo half-life and/or increased bioavailability, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 103

Claims 28, 54, and 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/30759 of record in view of Zetter of record (1998, Annu Rev Med. Vol. 49, pages 407-24).

Claims 28, 54, 55-57 are interpreted as drawn to nucleic acid encoding chimeric SA with endostatin or angiostatin as the inserted heterologous peptide. As stated above, the '759 patent teaches that a therapeutically useful angiogenesis-inhibiting protein or peptide could be inserted into a SA such that the resulting chimeric SA

polypeptide has higher in vivo half-life and other clinically beneficial properties. Note "tumoral angiogenesis" at page 4 line 9 and page 8 for advantage of inserting a therapeutically useful peptide in a SA.

The '759 patent does not specifically teach "angiostatin" or "endostatin".

However, Zetter of record (IDS filed on 4/30/2003, 1998, Annu Rev Med. Vol. 49, pages 407-24) teaches at page 414-5 that both angiostatin and endostatin are angiogenesis inhibiting proteins, and both are proven to be useful in treating cancer in vivo.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the claimed invention was made to make and use the claimed chimeric SA having either angiostatin or endostatin as the biologically active heterologous peptide with a reasonable expectation of success given the detailed teaching of how to make a chimeric SA at pages 9-30 of the '759 patent and also given the teaching of Zetter that angiostatin and endostatin are known before the effective filing date of the instant application. Further, Zetter teaches that those two angiogenesis inhibiting proteins are proven to be effective in vivo. Therefore, one of ordinary skill in the art would be motivated to make and use the instantly claimed product since the '759 patent teaches at pages 8 and 9 that the chimeric SA polypeptide will reduce the dosages administered, thus reduce side effect associated with administering a large dosage, and also because Zetter teaches that either angiostatin or endostatin has been proven to be effective in vivo cancer treatment.

Claims 28, 54, 55, and 84 are rejected under 35 U.S.C. **103(a)** as being unpatentable over as being unpatentable over WO 95/30759 of record in view of Cardarelli et al., of record (a copy provided with the previous Office action mailed on 5/28/2003, J Biol Chem, 1992 Nov 15, vol. 267, pages 23159-64).

Claims 28, 54, 55, and 84 are interpreted as drawn to nucleic acid encoding a chimeric SA with RGD peptide as the inserted heterologous peptide.

As stated above, the '759 patent teaches that a therapeutically useful peptide could be inserted into a SA such that the resulting chimeric SA polypeptide has higher in vivo half-life and other clinically beneficial properties.

The '759 patent does not specifically teach "RGD" as a therapeutically useful peptide.

However, Cardarelli et al., of record teach that RGD (note abstract for example) has been known in the art before the effective filing date of the instant specification, and also teach "The data suggest that specific inhibitors of collagen adhesion based on the **RGD** site can be designed. These compounds could **be valuable therapeutically in a number of disease**."

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the claimed invention was made to make and use the claimed chimeric SA having RGD as the biologically active heterologous peptide with a reasonable expectation of success given the detailed teaching of how to make a chimeric SA at pages 9-30 of the '759 patent and also given the teaching of Cardarelli et al., that RGD sequences are known before the effective filing date of the instant

application. Further, Cardarelli et al., teach that RGD could be valuable therapeutically in a number of disease. Therefore, one of ordinary skill in the art would be motivated to make and use the instantly claimed product since the '759 patent teaches at pages 8 and 9 that the chimeric SA polypeptide will reduce the dosages administered, thus reducing cost and also reducing painful injections and other inconveniences.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642